TABLE 1. *Production of nitric oxide and tumoricidal properties in mouse macrophages by liposomes containing MTP-PE, CGP31362 and JT3002*

Concentration of MLV (nmol/well)	MLV-HBSS		MLV-MTP-PE		MLV-31362		MLV-JT3002	
	NO (μM)	Cytotoxicity (%)	NO (μM)	Cytotoxocity (%)	NO (μM)	Cytotoxicity (%)	NO (μM)	Cytotoxicity (%)
50	8	4	4	19	28*	84*	30*	86*
25	5	0	2	14	26*	74*	29*	80*
12	1	1	2	10	23*	79*	23*	84*
6	1	2	2	5	22*	72*	22*	70*
3	1	0	2	4	20*	75*	22*	68*

Macrophages (1 x 10^5/well) were incubated with the indicated concentrations of MLV in medium containing 10 U/ml IFN-γ. All MLV contained 1 mg immunomodulator/300 μM phospholipids. NO production (nitrite/nitrate) was determined one day later. The cultures were washed and 1 x 10^4 [^{3}H]TdR-labeled A375P cells were added. Assays were terminated 72 h later. Macrophages incubated in medium alone (negative control) produced 0.2 μM NO and 10% cytotoxicity. Macrophages in medium containing LPS (1 μg/ml) and IFN-γ (10 U/ml) produced 26 μM NO and 48% cytotoxicity ($P<0.001$). The values are the mean of triplicate cultures. Variation from the mean did not exceed 10%. These are the results of one representative experiment of four.

*$P<0.001$.

TABLE 2. *Minimal concentration of liposome-JT3002 required to induce production of nitric oxide in murine macrophages*

Lipid concentration (nmol/well)	NO (μM			
	JT3002 (0.1 mg)	JT3002 (0.02 mg)	JT3002 (0.004 mg)	JT3002 (0.0008 mg)
25	27[a]	23[a]	10[a]	11
12.5	26[a]	20[a]	14[a]	9
6.2	24[a]	17[a]	12[a]	7
3.1	24[a]	16[a]	10	7
1.6	21[a]	13[a]	9	7
0.8	17[a]	11	9	7
0.4	19[a]	11	10	7
0.2	18[a]	10	10	6

Macrophages (1 x 10^5/well) were incubated in medium containing 10 U/ml IFN-γ (control) or medium containing 10 U/ml IFN-γ and different concentrations of liposomes containing 0.1 mg, 0.02 mg, 0.004 mg, or 0.008 mg JT3002 in 300 μM phospholipids. NO production was determined 24 h later. The values are the mean NO proudction in μM of triplicate cultures. Variation from the mean did not exceed 10%. Macrophages incubated with medium plus IFN-γ or medium containing IFN-γ plus LPS produced 9 and 25 μM NO, respectively. This is one representative experiment of three.

[a] $P<0.001$.

TABLE 3. *Activation of tumoricidal properties in macrophages from iNOS knockout mice*

Lipid concentration (nmol/well)	NO (μM)			Cytotoxicity (%)		
	+/+ mice	+/- mice	-/- mice	+/+ mice	+/- mice	-/- mice
50	21[a]	14[b]	0	93[a]	91[a]	7
25	20[a]	14[b]	0	93[a]	89[a]	1.5
10	17[a]	12	0	85[a]	62[a]	0
5	16[a]	11	0	31[a]	51[a]	0
0	0	0	0	0	0	0
LPS (1 μg/ml)	20[a]	13	0			

Macrophages (1 x 10^5/well) were incubated in medium containing 10 U/ml IFN-γ (control) or medium containing 1 μg/ml LPS (positive control), or medium containing different concentrations of MLV containing 0.1 mg JT3002/300 μM phospholipid. After 20 h incubation, the cultures were washed and 1 x 10^4 [^{3}H]TdR-labeled K-1735 M2 (shown) or CT-26 (not shown) cells were added. NO production (μM/10^5 macrophages) was determined after 20 h and cytotoxicity was determined after 72 h. The values are the mean of triplicate samples. Variation from the mean did not exceed 15%. This is one representative experiment of three.

[a] $P<0.01$.

[b] $P<0.05$.

TABLE 4. *Activation of tumoricidal properties in macrophages from LPS-responsive (C3H/HeN) and -nonresponsive (C3H/HeJ) mice*

Lipid concentration (nmol/well)	C3H/HeN mice		C3H/HeJ mice	
	NO (μM)	Cytotoxicity (%)	NO (μM)	Cytotoxicity (%)
20	23[a]	35[a]	32[a]	40[a]
2	11	28[a]	26[a]	32[a]
0.2	2	13	13	27[a]
0.02	5	7	9	11
0	2	3	0	6
LPS (1 μg/ml)	23[a]	36[a]	8	12

Macrophages (1 x 10^5/well) were incubated in medium containing 10 U/ml IFN-γ (control), or medium containing 1 μg/ml LPS (positive control), or medium containing different concentrations of MLV containing 0.1 mg JT3002/300 μM phospholipid. After 20 h incubation, the cultures were washed and 1 x 10^4 [^{3}H]TdR-labeled K-1735 M2 cells were added. NO production (nitrite) was determined after 20 h and cytotoxicity was determined after 72 h. The values are the mean of triplicate samples. Variation from the mean did not exceed 10%. This is one representative experiment of three.

[a] $P<0.01$.

TABLE 5. *Duration of tumoricidal activity in macrophages incubated with liposomes containing JT3002*

Days post-activation	NO (μM)		Cytotoxicity (%)	
	Medium	JT3002	Medium	JT3002
1	0.9	31.8[a]	5.9	49.7[a]
2	1.3	34.0[a]	6.6	19.8[b]
3	0.7	27.7[a]	4.1	19.2[b]
4	4.9	4.0	5.9	4.8
Reactivation				
5	2.2	33.7[a]	3.0	41.0[a]

Macrophages (1×10^5/well) were incubated in medium containing 10 U/ml IFN-γ (control) or medium containing 10 U/ml IFN-γ plus 1 nmol/well of MLV containing 0.1 mg JT3002/300 μM phospholipid. After 20 h incubation, the cultures were washed and fresh medium was added for 0, 1, 2, 3, or 4 days. At the different time points, 1×10^4 [^{3}H]TdR-labeled CT-26 cells were added. NO production (nitrite/nitrate) was determined at the indicated times. Cytotoxicity was determined after 72 h of continuous tumor-cell-macrophage interaction. The values are the mean of triplicate cultures. Variation from the mean did not exceed 10%. This is one representative experiment of two.

[a] $P<0.001$.

[b] $P<0.01$.

TABLE 7

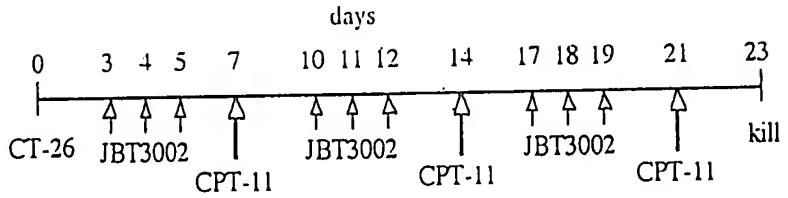
Combination Therapy of MTP-PE and CPT-11 for Mouse CT-26 Colon Cancer Liver Metastasis

Oral treatment	CPT-11	Spleen		Liver	
		Weight (g)	Tumor size (mm)	Weight	Median no. metastases
Saline	Saline	1.5 ± 0.1	1.4 ± 0.7	7.4 ±1.6	>100
Saline	50 mg/kg	0.6 ± 0.2	8.3 ± 2.0	2.0 ± 0.3	30
Saline	100 mg/kg	----------All mice died.----------			
MTP-PE	50 mg/kg	0.6 ± 0.2	10.4 ± 2	2.2 ± 0.7	30
MTP-PE	100 mg/kg	0.3 ± 0.1	5.6 ± 2	1.2 ± 0.1	4

Table 10. Therapy of experimental liver metastasis produced by murine CT-26 colon carcinoma with CPT-11 in combination with either MLV-JBT 3002 or free-form (FF) JBT 3002

Treatment	ΔBW[a] (%)	Spleen (primary)		Liver (metastasis)		
		Incidence	Tumor volume (mm^3)	Incidence	Median (range)	Liver weight (g)
MLV-HBSS	6.4	5/5	567 ± 94	5/5	46, 56, 72, >100, >100	3.5 ± 1.6
MLV-HBSS + CPT-11	-1.7	5/5	140 ± 30[c]	5/5	12, 15, 18, 39, 73	1.8 ± 0.3[b]
MLV-JBT3002 (1.0μg/dose) + CPT-11	-0.4	5/5	56 ± 29[c]	2/5	0, 0, 0, 6, 12	1.6 ± 0.2[b]
MLV-JBT3002 (0.1μg/dose) + CPT-11	-0.8	5/5	72 ± 15[c]	3/5	0, 0, 4, 8, 79	1.6 ± 0.2[b]
FF-JBT3002 (1.0μg/dose) + CPT-11	-3.9	5/5	202 ± 69[b]	5/5	7, 25, 37, 53, 81	1.8 ± 0.4[b]
FF-JBT3002 (0.1μg/dose) + CPT-11	0	5/5	85 ± 23[c]	3/5	0, 0, 9, 13, 35	1.5 ± 0.3[b]

Five BALB/c mice per group were given intrasplenic injection of 1×10^4 CT-26 cells on day 0. Mice were treated with repeated oral feedings of MLV-JBT3002 (at either 1.0 or 0.1 μg/dose, 5μmol PCPS MLV), or FF-JBT3002 (at either 1.0 or 0.1 μg/dose) thrice weekly for 3 weeks beginning 3 days after tumor cell inoculation, in combination with 100 mg/kg CPT-11 i.p. once a week (on day 7, 14, and 21). All groups were killed on day 23.



[a]The rate of body weight reduction was calculated with the formula: ΔBW (%) = (A B - 1) x 100, where A = mean body weights of mice at death, and B = mean body weights of mice on day 0.

[b]$P < 0.05$, [c]$P < 0.005$, compared with MLV-HBSS

Table II. Therapy of experimental liver metastasis produced by murine CT-26 colon carcinoma with CPT-11 in combination with either MLV-JBT 3002 or free-form (FF) JBT 3002

Treatment	ΔBW[a] (%)	Spleen (primary)		Liver (metastasis)		
		Incidence	Tumor volume (mm^3)	Incidence	Median (range)	Liver weight (g)
MLV-HBSS + saline	2.4	5/5	701 ± 268	5/5	54, >100, >100, >100, >100	4.2 ± 1.2
CPT-11	-1.5	5/5	189 ± 71[c]	5/5	22, 24, 39, 47, 57	1.7 ± 0.3[c]
MLV-JBT3002 (1.0μg/dose) + CPT-11	-1.4	5/5	154 ± 136[c]	3/5	0, 0, 3, 4, 13	1.4 ± 0.1[c]
FF-JBT3002 (1.0μg/dose) + CPT-11	0	5/5	238 ± 70[b]	5/5	5, 27, 31, 53, 80	1.7 ± 0.4[c]
FF-JBT3002 (0.1μg/dose) + CPT-11	1.7	5/5	290 ± 106[b]	5/5	1, 3, 10, 14, 34	1.5 ± 0.5[c]
FF-JBT3002 (0.01μg/dose) + CPT-11	-1.0	5/5	181 ± 115[c]	4/5	0, 1, 3, 14, 32	1.4 ± 0.4[c]

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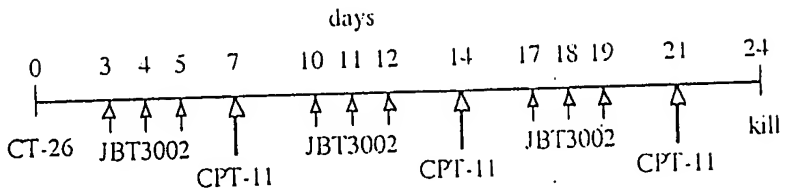
BALB/c mice were given intrasplenic injection of 1×10^4 CT-26 cells on day 0. Mice were treated with oral feedings of MLV-JBT3002 (at either 1.0 or 0.1 μg/dose, 5μmol PCPS MLV), or FF-JBT3002 (at either 1.0 or 0.1 μg/dose) thrice weekly for 3 weeks beginning 3 days after tumor cell inoculation, in combination with 100 mg/kg CPT-11 i.p. once a week (on day 7, 14, and 21). All groups were killed on day 24.



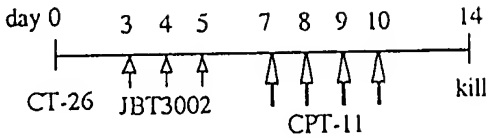
[a]Changes in body weight were calculated by the formula: ΔBW (%) = (A - B) B x 100, where A = mean body weight of mice at death, and B = mean body weight of mice on day 0.

[b]$P < 0.05$, [c]$P < 0.005$, compared with MLV-HBSS + saline

Table 12. Therapy of experimental liver metastasis produced by murine CT-26 colon carcinoma with intrasplenic injections in combination with either MLV-JBT 3002 or free-form (FF) JBT 3002 at different doses

Treatment	ΔBW[a] (%)	Spleen (primary) Incidence	Spleen (primary) Tumor volume (mm^3)	Liver (metastasis) Incidence	Liver (metastasis) no.	Liver weight (g)
MLV-HBSS + saline	5.1	5/5	153 ± 62	5/5	23, 26, 71, >100, >100	2.4 ± 1.0
MLV-HBSS + CPT-11	-17.6	5/5	52 ± 30	2/5	0, 0, 0, 1, 6	1.2 ± 0.1
MLV-JBT3002 (1.0μg/dose) + CPT-11	-1.5	5/5	45 ± 10	0/5	all 0	1.4 ± 0.1
FF-JBT3002 (1.0μg/dose) + CPT-11	-2.4	5/5	48 ± 8	2/5	0, 0, 0, 3, 5	1.4 ± 0.03
FF-JBT3002 (0.1μg/dose) + CPT-11	-2.2	5/5	50 ± 16	1/5	0, 0, 0, 0, 3	1.4 ± 0.2
FF-JBT3002 (0.01μg/dose) + CPT-11	0.4	5/5	29 ± 26	4/5	0, 2, 2, 26, 27	1.6 ± 0.1
FF-JBT3002 (0.001μg/dose) + CPT-11	-6.9	5/5	56 ± 25	1/5	0, 0, 0, 0, 3	1.4 ± 0.2
FF-JBT3002 (0.0001μg/dose) + CPT-11	-15.4	5/5	28 ± 20	3/5	0, 0, 1, 2, 5	1.1 ± 0.1

BALB/c mice were injected into the spleen with 1 x 10^4 viable CT-26 cells on day 0. Mice were treated with oral feedings of 5 μmol MLV-HBSS, MLV-JBT3002 (1 μg/dose), or FF-JBT3002 (at either 1.0, 0.1, 0.001, or 0.0001 μg/dose) for 3 consecutive days beginning 3 days after tumor cell inoculation. Seven days later, groups of mice received 4 daily i.p. injections of 100 mg/kg CPT-11. All groups were killed on day 14.

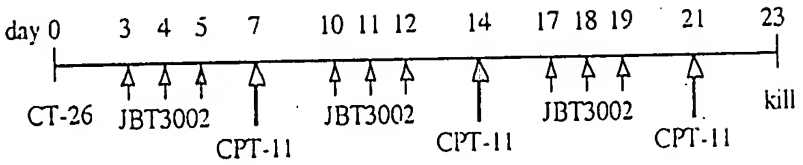


[a]Changes in body weight were calculated by the formula: ΔBW (%) = (A - B) B x 100, where A = mean body weight of mice at death, and B = mean body weight of mice on day 0.

Table 13. **Therapy of experimental liver metastasis produced by murine CT-26 colon carcinomas with once weekly CPT-11 injections in combination with either MLV-JBT 3002 or free-form (FF) JBT 3002 at different doses**

Treatment	ΔBW[a] (%)	Spleen (primary) Incidence	Spleen (primary) Tumor volume (mm^3)	Liver (metastasis) Incidence	Liver (metastasis) no.	Liver weight (g)
MLV-HBSS + saline	3.1	5/5	699 ± 322	5/5	89, >100, >100, >100, >100	4.1 ± 0.8
MLV-HBSS + CPT-11	1.2	5/5	334 ± 88	5/5	42, 42, 45, 56, 79	2.6 ± 0.3
MLV-JBT3002 (1.0μg/dose) + CPT-11	1.3	5/5	157 ± 96	4/5	0, 1, 9, 11, 13	1.5 ± 0.2
FF-JBT3002 (1.0μg/dose) + CPT-11	-1.4	5/5	235 ± 78	5/5	34, 41, 56, 70, 88	2.6 ± 0.6
FF-JBT3002 (0.1μg/dose) + CPT-11	-0.2	5/5	189 ± 13	5/5	3, 12, 16, 24, 34	1.6 ± 0.4
FF-JBT3002 (0.01μg/dose) + CPT-11	0.3	5/5	214 ± 45	5/5	2, 4, 13, 31, 40	1.6 ± 0.3
FF-JBT3002 (0.001μg/dose) + CPT-11	2.5	5/5	237 ± 20	5/5	31, 42, 47, 58, 69	2.8 ± 0.7
FF-JBT3002 (0.0001μg/dose) + CPT-11	2.3	5/5	225 ± 34	5/5	30, 32, 48, 52, 83	2.7 ± 0.9

BALB/c mice were injected into the spleen with 1 x 10^4 viable CT-26 cells on day 0. Groups of mice were treated with oral feedings of 5 μmol MLV-HBSS, MLV-JBT3002 (1 μg/dose), or FF-JBT3002 (at either 1.0, 0.1, 0.001, or 0.0001 μg/dose) thrice weekly for 3 weeks beginning 3 days after tumor cell inoculation. Some mice received an i.p. injection of 100 mg/kg CPT-11 once a week (on days 7, 14, and 21). All groups were killed on day 23.

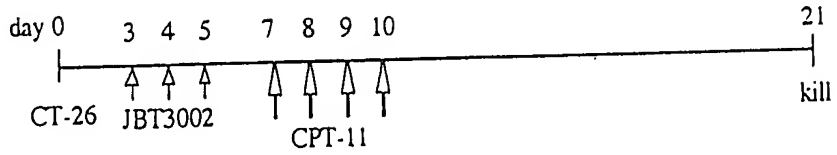


[a]Changes in body weight were calculated by the formula: ΔBW (%) = (A - B) B x 100, where A = mean body weight of mice at death, and B = mean body weight of mice on day 0.

Table IV. **Therapy of experimental liver metastasis produced by murine CT-26 colon carcinomas with intensive CPT-11 injections in combination with either MLV-JBT 3002 or free-form (FF) JBT 3002 at different doses**

Treatment	ΔBW_{14}[a] (%)	ΔBW_{21}[a] (%)	Spleen tumor		Liver metastasis		
			Incidence	Mean tumor volume (mm^3)	Incidence	No.	Liver weight (g)
Control	2.9	6.9	5/5	353 ± 29	5/5	54, >100, >100, >100, >100	3.4 ± 1.1
CPT-11	-24.0	ND	5/5[b]	35 ± 16	0/5[b]	all 0	1.2 ± 0.2
MLV-JBT 3002 (1.0 μg/dose) + CPT-11	-9.4	-7.6	5/5	75 ± 64	3/5	0, 0, 3, 5, 16	1.5 ± 0.1
FF-JBT 3002 (0.05 μg/dose) + CPT-11	-6.8	-6.0	5/5	83 ± 70	4/5	0, 1, 9, 18, 21	1.7 ± 0.0

BALB/c mice were injected into the spleen with 1×10^4 viable CT-26 cells on day 0. Mice were treated with oral feedings of 5 μmol MLV-JBT 3002 (1 μg/dose), or FF-JBT 3002 (0.05 μg/dose) for 3 consecutive days beginning 3 days after tumor cell inoculation. Seven days later, groups of mice received 4 daily i.p. injections of 100 mg/kg CPT-11. All groups were killed on day 21.



[a]Changes in body weight were calculated by the formula: $\Delta BW\ (\%) = (A - B)/B \times 100$, where A = mean body weight of mice on the indicated day , and B = mean body weight of mice on day 0.

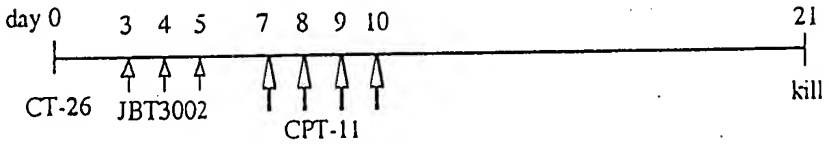
[b]All mice died during therapy (3 mice on day 15 and 2 mice on day 16).

ND, not determined.

Table 15. Therapy of experimental liver metastaswis produced by murine CT-26 colon carcinoma with intensive CPT-11 injections in combination with oral JBT 3002

Treatment	Spleen tumor		Liver metastasis			
	Incidence	Mean tumor volume (mm^3)	Incidence	No.	P^a	Liver weight (g)
Control	10/10	594 ± 51	10/10	85, >100, >100, >100, >100 >100, >100, >100, >100, >100		3.2 ± 0.9
CPT-11	6/10[b]	79 ± 38[c,e]	1/10[b]	0, 0, 0, 0, 0, 0, 0, 0, 0, 26	<0.0001	1.9 ± 0.3[c,d]
JBT 3002	10/10	88 ± 34[f]	9/10	0, 1, 2, 6, 10, 10, 11, 15, 22, 31	<0.0001	1.6 ± 0.2[e]
JBT 3002 + CPT-11	4/10	47 ± 26[f]	4/10	0, 0, 0, 0, 0, 0, 2, 5, 5, 8	<0.0001	1.4 ± 0.1[f]

BALB/c mice were injected into the spleen with 1 x 10^4 viable CT-26 cells on day 0. Groups of mice were treated with oral feedings of JBT 3002 (0.05 μg dose) for 3 consecutive days beginning 3 days after tumor cell inoculation. Seven days later, some mice received 4 daily i.p. injections of 100 mg/kg CPT-11. All groups were killed on day 21.



[a]As compared with control.

[b]Seven mice died during therapy (day 10, 13, 13, 14, 14, 17, 20).

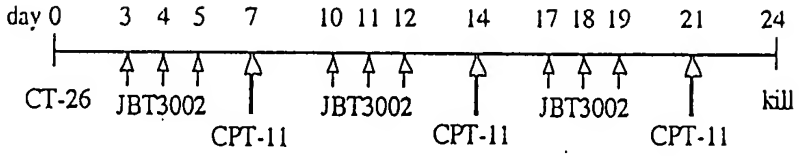
[c]Calculated from survive mice.

[d]$P<0.05$ as compared with control. [e]$P<0.001$ as compared with control. [f]$P<0.0001$ as compared with control.

Table 14. Therapy of experimental liver metastasis produced by murine CT-26 colon carcinoma with once weekly CPT-11 injections in combination with oral JBT 3002

Treatment	Spleen tumor		Liver metastasis			
	Incidence	Mean tumor volume (mm^3)	Incidence	No.	P^a	Liver weight (g)
Control	10/10	574 ± 101	10/10	72, >100, >100, >100, >100 >100, >100, >100, >100, >100		4.3 ± 1.0
CPT-11	7/10	116 ± 32[b]	8/10	0, 0, 1, 5, 6, 13, 33, 81, 85, >100	0.0005	2.0 ± 0.9[c]
JBT 3002	8/10	241 ± 84	9/10	1, 2, 50, >100, >100, >100 >100, >100, >100, >100, >100		4.2 ± 1.6
JBT 3002 + CPT-11	6/10	76 ± 34[b]	5/10	0, 0, 0, 0, 0, 1, 6, 7, 37, 57	<0.0001	1.7 ± 0.4[c]

BALB c mice were injected into the spleen with 1 x 10^4 viable CT-26 cells on day 0. Groups of mice were treated with oral feedings of JBT3002 (0.05 µg dose) thrice weekly for 3 weeks beginning 3 days after tumor cell inoculation. Some mice received an i.p. injection of 100 mg/kg CPT-11 once a week (on days 7, 14, and 21). All groups were killed on day 24.



[a]As compared with control.

[b]$P<0.05$ as compared with control. [c]$P<0.0001$ as compared with control.

Table 17. Induction of NO production in macrophages by free-form, formula 1, and formula 2 JBT 3002

1. Macrophages: TG-Mø from C57BL/6 mice.
2. Treatment of macrophages: Macrophages in 96-well plates (10^5/well) were incubated for 24 hr with JBT in the presence or absence of IFN-γ (10 U/ml). Nitrite in the culture medium was then determined.
3. Results:

JBT conc. (ng/ml)	Free JBT		Formula-1 JBT (pH 1.5-7)		Formula 2-JBT (pH 8)	
	medium	IFN-g	medium	IFN-g	medium	IFN-g
10	8.4	60.9*	2	50.7	2	47.4
2	0	53.1	0	38.6	0	38.1
0.4	0	44.7	0	34.8	0	33.5
0.08	0	41	0	25.5	0	20
0.016	0	33.7	0	6.3	0	1.9
0.003	0	17.5	0	0.4	0	0.7
0.0006	n.d.	n.d.	0	0.5	0	2
0	0	0.6				

- nitrite: μM.

LAL endotoxin test:

No endotoxin was detected in the free form JBT3002, Formula 1-JBT, and Formula 2-JBT at a concentration of 0.08 ng/ml of the reagent.

Table 17. Induction of NO production by JBT 3002.

1. Materials and Methods

1) Macrophages: C57BL/6 mice, TG-Mø, 10^5 cells/well in 96-well plate.
2) Treatment: with 10 U/ml of IFN-γ and various concentrations of JBT3002 for 24 hr in 200 µl/well MEM-5% FBS. Nitrite (100 µl/well) was measured.

2. Results

← TABLETS →

JBT3002 (ng/ml)	Free form		filtered		unfiltered	
	Medium	IFN-γ	medium	IFN-γ	medium	IFN-γ
10	0.5	47.1	0	41.0	7.0	53. 0
1	0	37.7	0	29.3	0	44.5
0.1	0	27.7	0	20.9	0	34.1
0.01	0	19.5	0	7.7	0	26.2
0.001	0	8.5	0	0	0	4.3
0.0001	0	0	0	0	n.d.	n.d.
0	0	0				

3. Endotoxin Test:

Endotoxin was not detected by the LAL assay in all of the three preparations of JBT3002 at concentration of 0.1 ng/ml.

4. CONCLUSION:

The contents in the tablet formulation did not alter the activity of JBT3002 in activation of macrophages in vitro.

Table 19A. Tumor weight and incidence of metastases of L3.6pl human pancreatic tumors in nude mice after 4 weeks treatment with 100 mg/kg CPT-11 i.p. once a week +/- oral feeding of JBT 3002 (tablet) 0.05 mcg/dose

Treatment start with CPT11: 7 days after orthotopic tumor cell injection
Treatment start with JBT3002: 3 days after orthotopic tumor cell injection

Treatment schedule:	wed	thurs	fri	sat	sun	mon	tues
	JBT3002	JBT3002	JBT3002	-	-	CPT11	-

(animals were sacrified 31 days after tumor cell injection)

	CPT11				CPT11 + JBT 3002			
animal	Tumor weight (mg)	Incidence			Tumor weight (mg)	Incidence		
		liver met	LN met	WT/PC		liver met	LN met	WT/PC
1	80	-	++	-	60	-	-	-
2	375	-	++	-	201	-	-	-
3	241	-	++	-	208	-	-	-
4	0	-	-	-	78	-	-	-
5	98	-	+	-	365	-	++	-
6	0	-	-	-	0	-	-	-
7	318	-	++	-	118	-	-	-
8	137	-	++	-	175	-	-	-
9	205	-	++	-	199	-	-	-
10	67	-	-	-	140	-	-	-
Median	117.5	0/10	7/10	0/10	157.5	0/10	1/10	0/10
Max	375				365			
Min	0				0			
Average	152.10				154.40			
St.Dev.	106.12				75.20			

Table 19B. Tumor weight and incidence of metastses of L3.6pl human pancreatic tumors in nude mice after 4 weeks treatment with 100 mg/kg CPT-11 i.p. once a week +/- oral feeding of JBT 3002 (tablet) 0.05 mcg/dose

Treatment start with CPT11: 7 days after orthotopic tumor cell injection
Treatment start with JBT3002: 3 days after orthotopic tumor cell injection

Treatment schedule:	wed	thurs	fri	sat	sun	mon	tues
	JBT3002	JBT3002	JBT3002	-	-	CPT11	-

(animals were sacrified 31 days after tumor cell injection)

	Control (HBSS)				JBT-3002			
animal	Tumor weight (mg)	Incidence			Tumor weight (mg)	Incidence		
		liver met	LN met	WT/PC		liver met	LN met	WT/PC
1	534	-	++	-	862	-	++	WT
2	556	-	++	WT/PC	871	-	+	-
3	483	-	++	-	981	+ (5)	++	WT
4	831	+ (1)	++	-	621	-	++	WT
5	955	+ (1)	+	-	362	-	+	-
6	73	+ (1)	++	-	733	-	++	-
7	578	-	++	-	559	-	-	-
8	723	++ (1)	++	-	820	+ (1)	+	-
9	701	-	++	WT	547	-	-	-
10		-	++	WT		-	-	-
Median	578	4/10	10/10	3/10	733	2/9	7/10	3/10
Max	955				981			
Min	73				362			
Average	603.78				706.22			
St.Dev.	176.64				163.53			

Table 17C. Tumor weight and incidence of metastases of L3.6pl human pancreatic tumors in nude mice after 4 weeks treatment with 100 mg/kg CPT-11 i.p. once a week +/- oral feeding of JBT 3002 (tablet) 0.05 mdg/dose

Treatment start with CPT11: 7 days after orthotopic tumor cell injection
Treatment start with JBT3002: 3 days after orthotopic tumor cell injection

Treatment schedule:	wed	thurs	fri	sat	sun	mon	tues
	JBT3002	JBT3002	JBT3002	-	-	CPT11	-

(animals were sacrified 31 days after tumor cell injection)

therapy	tumor weight in mg median (range)	Incidence liver met.	LN met.
Control (HBSS)	578 (73 - 955)	4/10	10/10
JBT3002	733 (362 - 981)	2/9	7/10
CPT11	117.5 (0 - 375)	0/10	7/10
CPT11+JBT3002	157.5 (0 - 365)	0/10	1/10

Table 29. Therapy of experimental liver metastasis produced by KM12SM human colon carcinoma with [illegible] plus oral JBT 3002 in nude mice

		7/20	7/27																			
Intensive		M	M	T	W	R	F	S	S	M	T	W	R	F	S	S	M	T	W	R	F	S	S
#5594 #5595	T																						
#5596 #5597	T						C	C	C	C													
#5598 #5599	T		J	J	J																		
#5600 #5601	T		J	J	J		C	C	C	C													
Once a week	M		M	T	W	R	F	S	S	M	T	W	R	F	S	S	M	T	W	R	F	S	S
#5602 #5603	T																						
#5604 #5605	T						C (75)							C 5604: 75 5605: 50							C		
#5606 #5607	T		J	J	J					J	J	J					J	J	J				
#5608 #5609	T		J	J	J		C(75)			J	J	J		C 5606: 75 5609: 50			J	J	J		C		

T: KM12sm 1x10^6 i.spl
J: FF-JBT3002 (0.05mcg/dose) oral
C: CPT-11 (50mg/kg) i.p.

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Table 21. Therapy of experimental liver metastases produced by CT-26 murine colon carcinoma with CPT-11 i.p. plus oral JBT 3002 (free-form or tablet) in BALB/c mice

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				0				7						14						21		
				F	S	S	M	T	W	R	F	S	S	M	T	W	R	F	S	S	M	T	W	R	F	S	S	M
INTENSIVE TREATMENT																												
Group I	(n=5)	Control	7332	T																								
II	(n=5)	CPT-11	7333	T							C	C	C	C														
III	(n=5)	FF-JBT	7334	T			J	J	J																			
IV	(n=5)	TAB-JBT	7335	T			J	J	J																			
V	(n=5)	FF-JBT/CPT-11	7336	T			J	J	J		C	C	C	C														
VI	(n=5)	TAB-JBT/CPT-11	7337	T			J	J	J		C	C	C	C														
ONCE A WEEK TREATMENT																												
Group I	(n=5)	Control	7338	T																								
II	(n=5)	CPT-11	7339	T							C					C					C							
III	(n=5)	FF-JBT	7340	T			J	J	J				J	J	J				J	J	J							
IV	(n=5)	TAB-JBT	7341	T			J	J	J				J	J	J				J	J	J							
V	(n=5)	FF-JBT/CPT-11	7342	T			J	J	J		C		J	J	J		C		J	J	J		C					
VI	(n=5)	TAB-JBT/CPT-11	7343	T			J	J	J		C		J	J	J		C		J	J	J		C					

Legend

T: CT26, 10,000 cells, i.spl (by Shinohara and Ozawa)

C: CPT-11, 100 mg/kg, i.p. (by Shinohara and Ozawa)

J: JBT 3002 (free form or tablet solution), 0.05 mcg/dose, oral (by Jerry)

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